

Bandolier has long had the ambition to avoid seeing her GP except socially. That involves examining the evidence about healthy living, and was one reason why the *Bandolier* Internet site has gathered together lots of good evidence about healthy living. In the end it comes down to three things: a good diet with lots of vegetables and antioxidants, including the odd tipple, a decent amount of exercise, and avoiding seriously risky behaviours like riding motorcycles, hang-gliding, and smoking.

Those of you enjoying your hols in and around the Med will probably be able to experience the delights of a Mediterranean diet. Think of it as a touch of evidence-gathering, and we have some really good evidence that a Mediterranean diet prevents problems in those of us without coronary heart disease, and helps those of us with CHD to keep its worst ravages at bay.

Internet Bandolier

Readers who enjoy a quiet surf of the Internet might like to take a look at the *Bandolier* site. It was completely revised in July to be faster and easier on the eye. In addition there are a host of downloadable goodies from *Bandolier Extra*.

In recent months there have been three new postings that might be of interest - on needlestick injuries, on acute pain, and on calculating and using NNTs.

Paper Bandolier

A word of thanks to those of you who renewed subscriptions recently. *Bandolier* gets no direct funding from government coffers, and support from subscriptions goes a long way to helping to keep it afloat.

Those of you with the ear of those important people who run NHS organisations might like to remind them that bulk orders for *Bandolier* from the NHS are supplied at little more than cost price, a price that hasn't changed for 10 years.

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MEDITERRANEAN DIET EVIDENCE

To some summer visitors to the shores of the Mediterranean, a Mediterranean diet might be thought to consist of lager and burgers, just in larger quantities than usual. To most of us it is more like a Greek salad with lots of olive oil, grilled fish, and some fruit, all washed down with the odd bottle of vino. There are big differences in the diet, and, since we are what we eat, big differences in what that diet does for us.

Much has been written on the benefits of Mediterranean diets, and the particular components that make it better. Recent large observational [1] and randomised [2] studies make understanding just a bit easier.

Observational study [1]

This was an examination of 22,000 Greek adults aged 20 to 86 years from all parts of Greece. Dietary intake for the year before enrolment was obtained by a questionnaire delivered by trained interviewers, and examined frequency and amount of food with photographs for estimation of usual portion sizes. The daily intake of 14 food groups or nutrients was obtained in grams per day for each participant.

Adherence to a Mediterranean style diet was determined with reference to some of these food groups, by the simple expedient of whether an individual consumed more or less than the median for their sex (Table 1). Possible scores were 0-9.

Individuals were followed up for a median of 44 months, and the date and cause of death for any participant obtained from death certificates and other sources. Observers blinded to the diet score of individuals adjudicated outcomes.

Results

There were 22,000 people with full details available. There were significantly fewer deaths among women than men, and more deaths in people over 55 years than in those under 55 years, and in current smokers, but fewer deaths in people who took more exercise.

Death rates in women and men were higher in those with a low diet score of 0-3 (1.7%) than in those with diet score of 4 and above (1.0%). Figure 1 shows the death rates per 10,000 person-years at different Mediterranean diet scores. Adherence to the diet involved large differences for the propor-

Table 1: Components of Mediterranean diet score for men and women

Diet components	Median (grams/day)		Score	
	Men	Women	Above median	Below median
Beneficial components				
Vegetables	550	500	1	0
Legumes	9	7	1	0
Fruits and nuts	360	360	1	0
Cereal	180	140	1	0
Fish	24	19	1	0
Monosaturated:saturated lipid ratio	1.7	1.7	1	0
Detrimental components				
Meat and poultry	120	90	0	1
Dairy products	200	190	0	1
Alcohol consumption	10-50	5-25	1	1

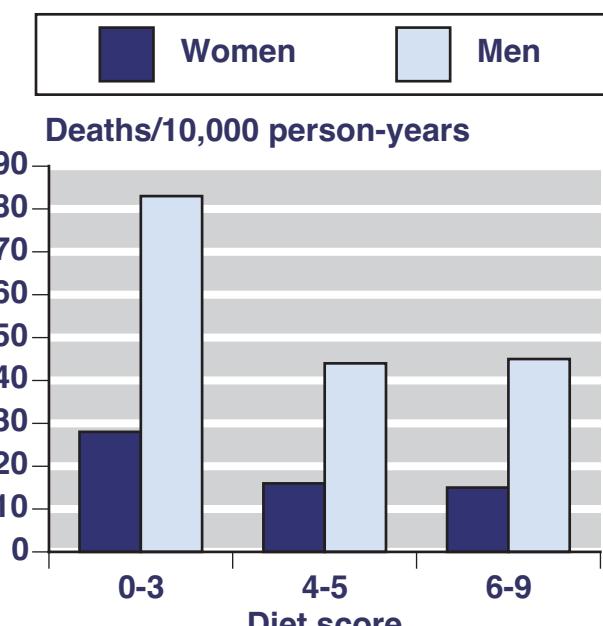
Note that 25 grams of alcohol is about two drinks a day, and that higher ratios of mono-unsaturated to saturated fat indicate larger consumption of olive oil

tions above and below the median. For example, Figure 2 shows olive oil consumption among women with different diet scores, and Figure 3 shows vegetable consumption among men with different diet scores. Similar results obtained for legumes, fruit and nuts, fish, cereals, dairy products and monounsaturated to saturated fat ratios, but not for meat.

A two point increment in the Mediterranean diet score reduced the risk of death by about 25%. Effects were important for older people, those taking less exercise, and any level of BMI, as well as cause of death or coronary heart disease or cancer.

Over an average of 3.7 years, a population aged 20 to 86 years with a Mediterranean diet score of 4 or more would have one fewer death for every 140 people (95% confidence interval 94 to 276) than a similar population with a score of 3 or below.

Figure 1: Death rate by diet score



Randomised trial [2]

A randomised trial examined the dietary intervention of an Indo-Mediterranean diet consisting of a control group using the National Cholesterol Education Programme step 1 diet and the same diet with additional recommendations to consume every day at least:

- ◆ 400-500 grams of fruit, vegetables or walnuts or almonds a day,
- ◆ 400 -500 grams of whole grains,
- ◆ mustard seed or soy bean oil.

The aim was to provide plenty of phytochemicals, antioxidants and alpha-linoleic acid.

Patients were Indians with a documented history of coronary artery disease, and randomisation was stratified by

Figure 2: Olive oil consumption by diet score

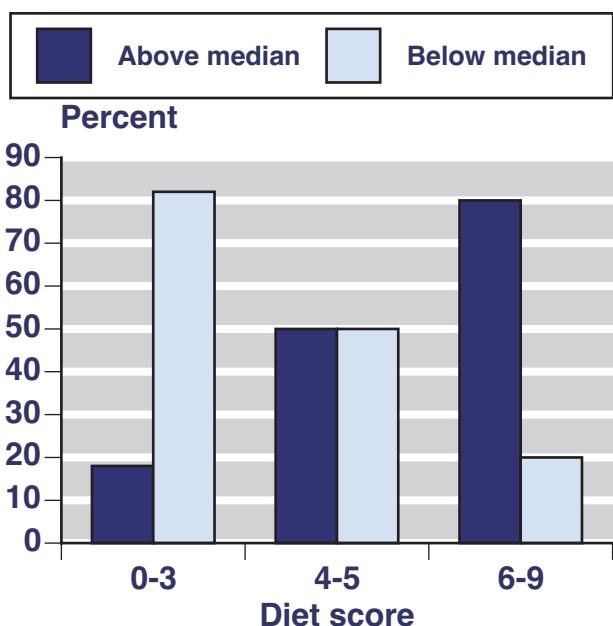
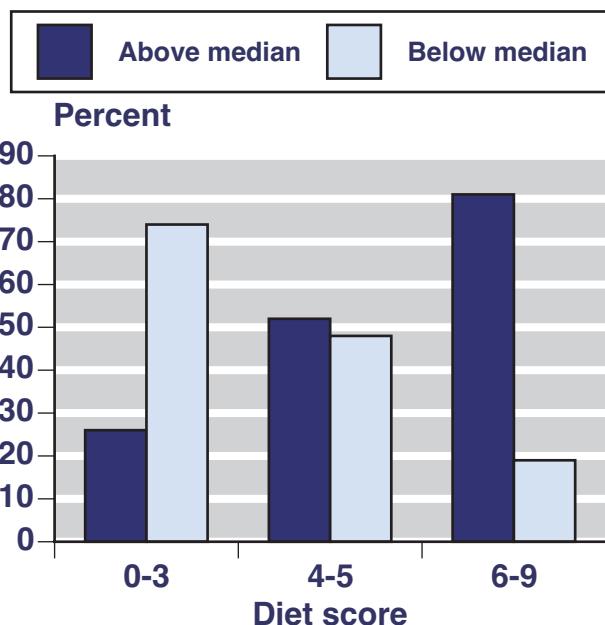


Figure 3: Vegetable consumption by diet score



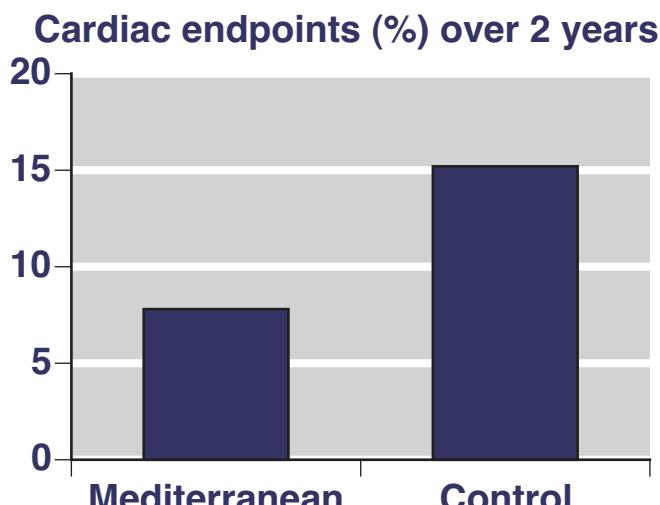
risk factors. Follow up was for two years, and the principle outcomes were fatal or nonfatal myocardial infarction, sudden cardiac death, and the combination of these outcomes.

Results

Each group contained almost 500 patients, and the groups were comparable at baseline for risk factors and treatments. Their average age was 49 years. Most patients had serum cholesterol between 6.2 and 6.7 mmol/L, and about half were smokers at entry. About 30% were overweight or obese.

The combined outcome occurred in 39/499 (8%) patients on the Indo-Mediterranean diet and 76/501 (15%) on the NCEP diet (Figure 4). The adjusted rate ratio was 0.5 (0.3 to 0.7), and reductions were similar for all components of the combined outcome. For every 14 (95% confidence interval 9 to 29) patients randomised to an Indo-Mediterranean diet for two years, one fewer had a fatal or nonfatal myocardial infarction or sudden cardiac death than similar patients using a standard NCEP diet.

Figure 4: Total cardiac endpoints for Indo-Mediterranean diet and control diet



While significant reductions in total and LDL cholesterol and triglycerides occurred in both groups, the reductions were much larger in those on the Indo-Mediterranean diet. After two years, these patients had reduced their total cholesterol by 0.7 mmol/L, compared with 0.2 mmol/L in control patients.

Other secondary clinical outcomes occurred significantly less frequently with the Indo-Mediterranean diet, including angina, a positive exercise test, left ventricular hypertrophy and heart failure. There were 49 cardiovascular events. Angiography, angioplasty or bypass surgery happened in 49 (10%) of people on the Indo-Mediterranean diet compared with 96 (19%) on the control diet, with an NNT of 11 (7-20).

Comment

These are two terrific studies, with different study architectures, and conducted in different people in different parts of the world. They come to much the same conclusion, that a diet rich in fruits, nuts, vegetables, fish and mono-unsaturated vegetable oils, and with limited dairy products and meat, is good for the heart. The odd glass of wine helps those of us who want to partake. The fact that they come to much the same conclusion is important, because it gives us more confidence in the results and the conclusion that a Mediterranean diet is a good thing.

The gains are not trivial. The setting of the randomised trial was that of secondary prevention, where we expect NNTs over five years for statins of about 10-20 (Bandolier 47). The Indo-Mediterranean diet had an NNT of 14 over two years, equivalent to an NNT of 5-6 over five years if the effect continued over that time. And in the observational Greek study, an NNT of 140 over 3.7 years comes down to about 10 over our 50 years or so of life as an adult.

Nor is this a particularly hard goal for most of us. The randomised trial [2] claims that the Indo-Mediterranean diet is economical, and can be produced by farmers at a cost of about US\$1 per day. It may cost some of us a tad more at our local supermarket, but even so it is hardly likely to break the bank.

The take home message is that diet is a powerful agent for reducing our chances of dying young, or having heart disease. That message is just as important for those who already have heart disease as those who do not. For some folk access to components of a Mediterranean diet will be difficult, as it was for most of us before the advent of supermarkets and year-round fruit and vegetables. For most of us there's just no excuse any more.

References:

- 1 A Trichopoulou et al. Adherence to a Mediterranean diet and survival in a Greek population. *New England Journal of Medicine* 2003 348: 2599-2608.
- 2 RB Singh et al. Effect of an Indo-Mediterranean diet on progression of coronary artery disease in high risk patients (Indo-Mediterranean diet heart study): a randomised single-blind trial. *Lancet* 2002 360: 1455-1461.

HOW MANY CHD PATIENTS ARE THERE?

One of the main priorities of the UK National Service Framework for coronary heart disease is secondary prevention in patients with preexisting coronary heart disease. To do this, patient registers are clearly needed to ensure that advice and treatment according to best evidence can be delivered effectively. A knowledge of prevalence, and how to develop and run registers is needed. A study from south London in a large population provides some answers and key pointers [1].

Study

The setting was 69 practices with a population of 380,000 patients, of whom 104,000 (27%) were over 44 years of age. Participation was high, with 63 practices and 92% of the population participating. Most (80%) of the practices used a single computer record system (EMIS). Data were collection between September 2000 and May 2001.

Patients were identified by searching records for particular codes or prescriptions of cardiovascular drugs. Some records were hand searched. An age limit of over 44 years was set because CHD is rare in younger patients.

There had to be a confirmed diagnosis of CHD with supporting evidence from diagnostic tests, procedures like coronary revascularisation, or documentary evidence from hospital correspondence. Information was also obtained about risk factors and blood pressure and cholesterol recording, and current treatment.

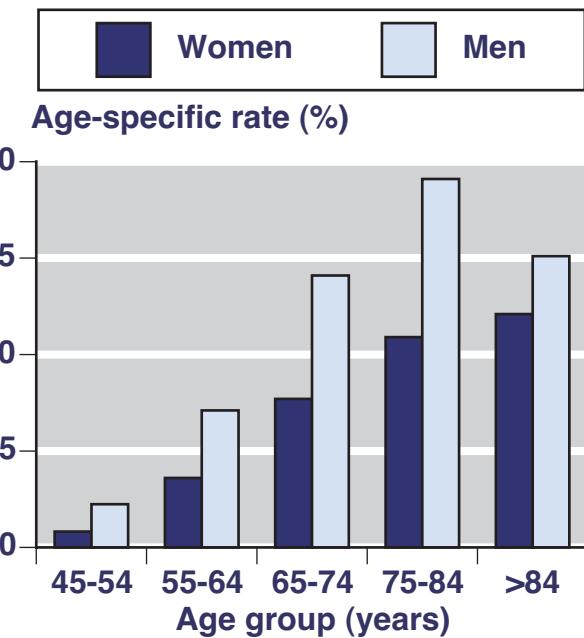
Results

There were 6,800 patients both over 44 years and with CHD, with crude prevalence rates of 8.0% in men and 5.2% in women. Age-specific prevalence is shown in Figure 1.

Table 1: Recording of risk factors in primary care in south London - percentage of CHD patients with risk factor recorded or with poorly-controlled risk factor (shaded)

Variable	Percent of CHD patients	
	Women	Men
Blood pressure recorded in previous 5 years	90	89
Blood pressure above optimal	2 7	2 6
Any cholesterol recorded	55	64
Cholesterol recorded in previous 2 years	44	51
Cholesterol above 5 mmol/L	5 9	4 4
BMI recorded in previous 2 years	34	34
BMI above 30 kg/sq metre	2 9	2 6
Smoking status recorded in previous 2 years	31	31
Current smoker	2 1	2 5
Prescribed statin	38	49
Prescribed aspirin	59	65

Figure 1: Age-specific prevalence of CHD in women and men



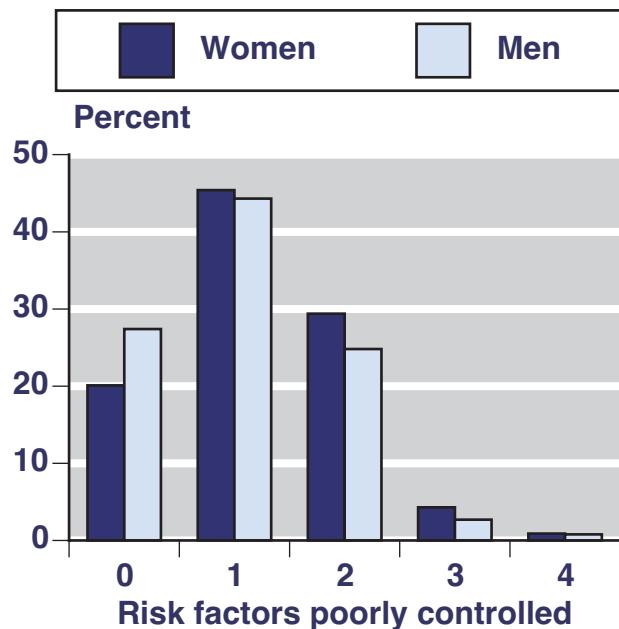
Recording of risk factors was not complete (Table 1). While most of these patients had blood pressure recorded in the previous five years, cholesterol, BMI and smoking status recording was less than complete. Nor was control complete. Substantial minorities of patients had above optimal blood pressure and cholesterol.

In a subgroup of practices it was possible to examine how well multiple risk factors were controlled. Most patients had at least one risk factor poorly controlled (Figure 2). Prescribing of statins and aspirin was higher in men than in women (Table 1).

Comment

There were two main messages. First, this gives a handle on just how many patients in a UK primary care population have coronary heart disease. There will be about 2,100

Figure 2: Percentage of women and men with poorly controlled risk factors



per 100,000 population, given that the population in this study were younger than the UK average. Second, it tells us that at the beginning of 2001 a significant proportion had multiple risk factors that were poorly controlled. Initiatives like the NSF and new incentives for primary care were designed to help reduce this deficit.

The authors, though, make a telling comment, that general practices need help to make the best use of their computer systems to facilitate the collection of data for registers, like this CHD register. IT plus evidence plus incentives should begin to make a difference, and get the evidence into practice. It will also help organisations make an informed estimate about the likely burden of disease and the costs likely to be incurred in guideline implementation.

References:

- 1 K Carroll et al. Prevalence and management of coronary heart disease in primary care: population-based cross-sectional study using a disease register. *Journal of Public Health Medicine* 2003; 25: 29-35.

SMOKING WITH CHD

All of us deal with risk every day. If you drive on the roads in the UK, you accept a (roughly) 1 in 18,000 chance of dying in a road accident in one year. Given the volume of traffic on our roads, that is a risk most of us are willing to accept. But it is not an unthinking acceptance, because many of us try to minimise the risk by driving carefully, and especially by buying safer cars with air bags and crumple zones. Indeed, with cars having a greater longevity than ever, buying a new car may have more to do with safety than reliability, unless you live next door to someone called Jones.

Yet we shrug off much greater risks. Otherwise why would so many of us smoke? A defining moment for many smokers can be surviving a heart attack, when the folly of our behaviour strikes home, and smoking is given up. Others take the more fatalistic view that the damage is already done, or they need a little pleasure in life. A new systematic review [1] tells us the fatalistic view just ain't so, and that smokers with coronary heart disease have an extra 1 in 10 chance of dying over five years because of their smoking.

Systematic review

The review sought studies with patients diagnosed with previous heart attack, or stable or unstable angina and who were smoking at baseline with smoking status well defined. Prospective cohort studies had to include current smokers at baseline, with smoking status measured to find who had quit smoking, in which the follow up was at least two years and with all cause mortality as an outcome measure.

The search strategy was extensive, examining nine electronic databases, and studies were not restricted by language.

Results

There were 20 included studies with 12,600 patients, mostly using data collected in the 1960s and 1970s. Most cases were men (80%), and average cessation rate was 45%. Follow up ranged from two to 26 years, though most studies reported follow up of three to seven years, with a mean of five years.

Most studies involved follow up hospital case series, and reporting of smoking status was usually at some follow up appointment, though it was not validated, for example by biochemical measurement, in most studies. Most studies had a clear definition of the cardiac event. Loss to follow up was usually small. Size varied from under 100 to over 4,000 patients.

Figure 1: Death rates in patients with CHD who continued smoking, or who quit

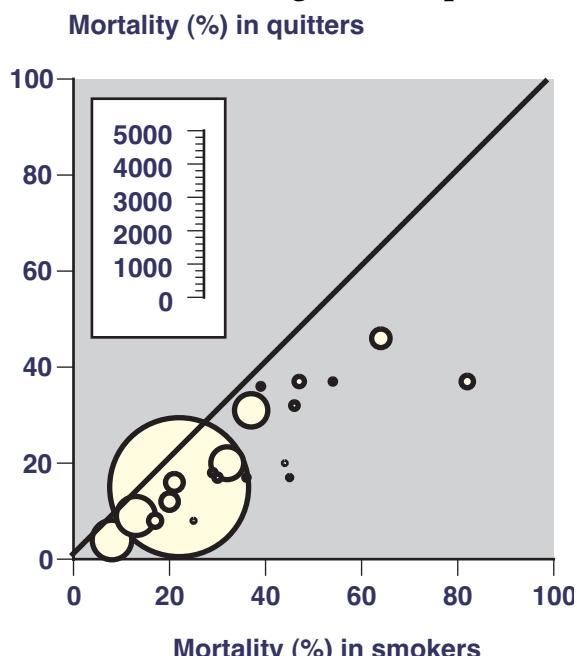


Table 1: NNTs to prevent one death or reinfarction over five years by CHD patients quitting smoking compared with continuing to smoke

Event	Number events/total (%)		Relative risk (95% CI)	NNT (95% CI)
	Quitters	Smokers		
Death (all studies)	1044/5649 (18)	1884/6944 (27)	0.64 (0.58 to 0.72)	12 (10 to 14)
Death (better studies)	645/3371 (19)	1294/5027 (26)	0.71 (0.65 to 0.77)	15 (12 to 21)
Nonfatal reinfarction	263/2467 (11)	516/3622 (14)	0.68 (0.57 to 0.82)	28 (19 to 52)

There were fewer deaths in quitters (18%) than in people who continued to smoke (27%), and the degree of reduction was consistent across all death rates reported (Figure 1). Results were broadly similar in all studies, and in six higher quality studies with about two-thirds of all patients (Table 1). Higher quality here was defined by a sample size of 500 smokers at baseline, with fewer than 15% dropouts, and with adequate or good control of confounding.

A secondary outcome was nonfatal reinfarction, and while this was a less frequent event, the same degree of reduction was seen (Table 1).

Relative risk was reduced by about 30%, and the absolute risk by about 9% for mortality, translating into a number needed to treat of about 12 for one additional nonsmoking patient to be alive at five years.

Comment

This is a good review. It gives the consistent and unequivocal answer that smoking remains harmful after a coronary event. Carrying on smoking carries a five year risk of 1 in

10 of dying because you smoke. By contrast, the risk of dying on the roads over five years would be more like 1 in 4000. Smoking in those circumstances is 400 times more dangerous than driving.

Also interesting in the review is the discussion about limitations, and how limitations may affect the result. Most of them make the results more conservative. For instance, if people who said they had stopped smoking were lying, the quitter results would be worse than they should be, and the benefits of stopping smoking under-estimated.

There's another point here. The word quit is one with negative connotations, with dictionary definitions of releasing from obligation, or clearing off, as well as to leave off, which is what is meant in this context. A thesaurus gives alternatives like deliver, free, or liberate. Perhaps it is time to look for an alternative description of people who stop smoking, less clearing off and more deliverance, perhaps.

References:

- JA Critchley, S Capewell. Mortality risk reduction associated with smoking cessation in patients with coronary heart disease. A systematic review. *JAMA* 2003; 290: 86-97.

FINASTERIDE TO PREVENT PROSTATE CANCER?

It was John Maynard Keynes who commented that "in the long run we're all dead". He also said that "I would rather be vaguely right than precisely wrong". We might apply both of these to prostate cancer and its prevention. We know that it is the commonest of cancers in men, but that far more men have it than die from it, because of the variable biology and course of the disease. It is a disease of older men, and while we have various treatments for it, that begs an interesting question of whether we can prevent it.

Given that there is some evidence that androgens influence the development of prostate cancer, one strategy might be to use 5 alpha-reductase inhibitors to inhibit conversion of testosterone to the more potent androgen dihydrotestosterone to examine whether reduced androgen levels in the prostate would reduce the risk of prostate cancer. A systematic review of finasteride in BPH in trials up to four years found no evidence in support of reduced prostate cancer rates [1]. A large two-year randomised trial of the newer agent dutasteride [2] did find a significant reduction (from 1.9% to 1.1%), though with only 66 cases.

How might an investigation of prostate cancer prevention be done? It would need to be large, and of a long duration. It would need to have a placebo arm, and have good working definitions of prostate cancer both during the study, and at the end of the study. It would need to record other clinical and adverse events. A randomised trial doing just that [3] has recently reported that finasteride does reduce prostate cancer, but not without some cost in adverse events.

Study

The study enrolled men aged 55 years or older with a normal digital rectal examination, and American Urological Association score of 20 or lower (less than severe symptoms of benign prostatic hyperplasia), and a PSA of 3.0 µg/L or lower. Men were given a three-month supply of placebo tablets, and if PSA was confirmed as being 3 µg/L or lower and adherence was with 80% of nominal, they were randomised to finasteride 5 mg/day or placebo.

The planned duration was seven years, with twice yearly visits for supply of medicine, pill counts and recording of clinically significant events and adverse events. Because finasteride affects PSA levels, an end of study biopsy was planned for men without a diagnosis of prostate cancer. The size of the study was planned with loss to follow up and refusal of end of study biopsy assumptions built in.

The primary outcome was men with diagnosis of prostate cancer or who underwent end of study prostate biopsy as the intention to treat population. All PSA levels of men on finasteride were corrected by multiplying by 2.3 to account for the effects of finasteride of PSA levels. All PSA measurements and biopsy histology analyses were performed in a central laboratory.

Results

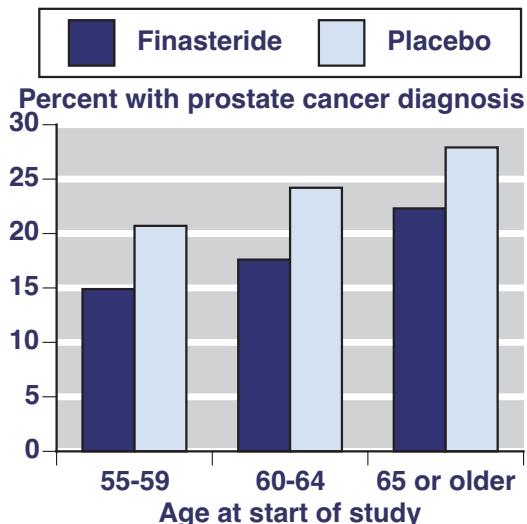
The number of men randomised was 18,880, most during the first year. The study was terminated early because of the statistical significance of the results at interim analysis, but 86% of men had completed seven years of treatment at the time of the analysis.

Prostate cancer

In the intention to treat cohort of 9,060 men, prostate cancer was diagnosed during the study or at end of study biopsy in 18% of men on finasteride and 24% of men on placebo (Table 1). The number needed to treat with finasteride 5 mg a day for seven years to prevent a diagnosis of prostate cancer in one of them was 17 (95% CI 13 to 23).

Similar efficacy was seen in men with a diagnosis for cause (clinical suspicion of cancer) during the trial or at the end of the study and in those in whom cancer was diagnosed at the end of study biopsy (Table 1) [note that some men might be included in both of these definitions]. Similar efficacy

Figure 1: Prostate cancer diagnosis by age at start of treatment, and treatment



was seen in younger and older men (Figure 1), at different levels of starting PSA, and in men with or without prostate cancer in a first-degree relative (though cancer rates were lower in men without an affected relative; Figure 2).

With finasteride, cancers diagnosed were more likely to be of higher grade, with Gleason scores of 7-10 (Figure 3). Most prostate cancers were clinically localised, in 98% of cases in both groups. In men who had an end of study biopsy that was not for cause and who had both a tumour and a PSA of 2.5 µg/L or less, 15% of the tumours were of high grade.

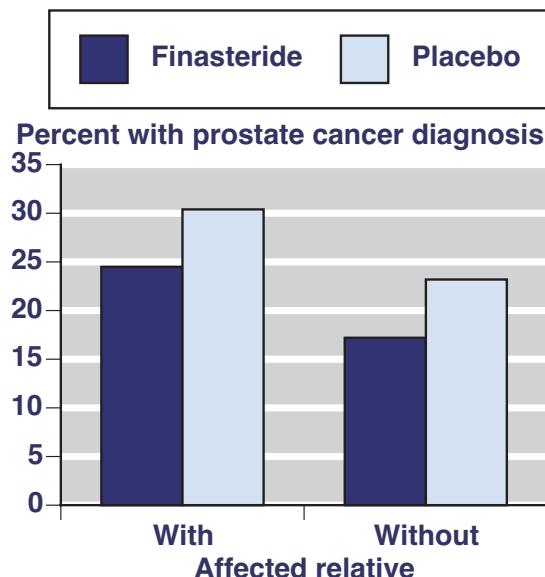
Other clinical events

Other prostate and urinary clinical events occurred less frequently with finasteride than with placebo (Table 1). The largest effect was the development of benign prostatic hyperplasia, with a number needed to treat of 28 (24 to 36) to

Table 1: Outcomes of prostate cancer diagnosis, other clinical outcomes, and adverse events with seven years of treatment with finasteride 5 mg daily

Outcome	Men	Percent with		Relative benefit	(95% CI)	NNT
		Finasteride	Placebo			
Cancer						
Cancer diagnosed at any time	9060	18	24	0.8 (0.7 to 0.9)	17 (13 to 23)	
Cancer diagnosed for cause during or at end of trial	3573	27	30	0.9 (0.8 to 1.0)	34 (17 to 2700)	
Cancer diagnosed at end of study biopsy	7472	10	15	0.7 (0.6 to 0.8)	20 (15 to 29)	
Other clinical outcomes						
Benign prostatic hyperplasia	18880	5.2	8.7	0.6 (0.5 to 0.7)	28 (24 to 36)	
Increased urinary urge or frequency	18880	13	16	0.8 (0.7 to 0.9)	41 (29 to 71)	
Urinary retention	18880	4.2	6.3	0.7 (0.6 to 0.8)	48 (37 to 69)	
Prostatitis	18880	4.4	6.1	0.7 (0.6 to 0.8)	60 (44 to 98)	
Transurethral resection of prostate	18880	1.0	1.9	0.5 (0.4 to 0.7)	113 (82 to 184)	
Urinary tract infection	18880	1.0	1.3	0.7 (0.6 to 0.9)	390 (150 to 670)	
Adverse events						
Men	Finasteride	Placebo	Relative risk	NNH		
Reduced ejaculate volume	18880	60	47	1.28 (1.25 to 1.31)	7.6 (6.9 to 8.6)	
Erectile dysfunction	18880	67	60	1.13 (1.11 to 1.15)	13 (11 to 16)	
Loss of libido	18880	65	60	1.10 (1.08 to 1.12)	17 (14 to 23)	
Gynaecomastia	18880	4.5	2.8	1.6 (1.4 to 1.9)	57 (44 to 81)	

Figure 2: Prostate cancer diagnosis by affected relative, and treatment



prevent one case. Urinary retention (NNT 48) and operations for prostate resection (NNT 113) were also significantly less common with finasteride than with placebo. Mean prostate volume was 26 cc in the finasteride group compared with 34 cc in the placebo group.

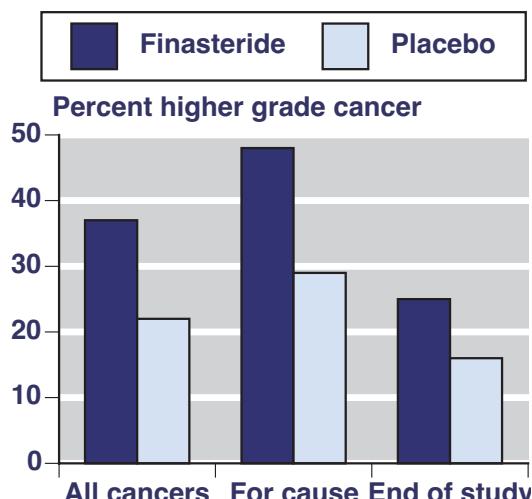
Adverse events

Adverse events relating to sexual function occurred more frequently with finasteride than with placebo (Table 1). The largest difference was for reduced ejaculate volume with a number needed to harm of 7.6 (6.9 to 8.6). Erectile dysfunction and loss of libido affected 5-7% more men with finasteride than placebo, and gynaecomastia was also more frequent.

Comment

The lifetime risk of prostate cancer is about 1 in 6, which makes preventive measures attractive. Healthy living is an obvious first, and therapeutic prevention a second, choice. Treatment with finasteride 5 mg a day for seven years prevented prostate cancer diagnosis in one man for every 17

Figure 3: Gleason score 7-10 prostate cancer diagnosis



treated. Is finasteride preventing prostate cancer, or treating it? The effects were seen early, and there is at least a hint that finasteride may be treating subclinical microscopic cancer as well as delaying the onset of prostate cancer. That might accord with the finding of higher grades of cancer with finasteride, but there are many possibilities and opinions that these data do not address.

There were additional benefits with finasteride. Shrinking the prostate brought benefits like reducing the diagnosis of benign prostatic hyperplasia, and urinary retention and need for surgery. But there were also harms, notably related to the known adverse effects of finasteride on sexual function.

So choosing this as a strategy for practice is a bit early, perhaps, though it is certainly a major first step in thinking about cancer prevention. And then there's the little matter of cost. We would need to treat 17 men with finasteride for seven years to prevent a prostate cancer diagnosis in one of them. The drug costs at 2003 prices would be about £38,500 to achieve that. But finasteride will come off patent in the next few years, and lower generic prices could reduce that substantially, unless that is a vain hope.

What about looking at it from the point of view of an individual man, weighing up the benefits and risks? At 55 years old, and with no affected relatives, the chance of diagnosis of prostate cancer from the overall trial results is about 20 in 100 over the next seven years. But only about 40% of the diagnoses were made for cause during the seven years. Some of the cancers might never proceed to clinical diagnosis. That reduces the individual risk to 8 chances in 100. Balanced against possible earlier loss of sexual potency, treatment might not be a good choice. For an older man with an affected relative, a moderate prostate symptom score and less interest in sexual potency, treatment might make sense. It's all a question of how vaguely we are right.

References:

- 1 JE Edwards, RA Moore. Finasteride in the treatment of clinical benign prostatic hyperplasia: a systematic review of randomised trials. *BMC Urology* 2002; 2: 14 (<http://www.biomedcentral.com/1471-2490/2/14>)
- 2 CG Roehrborn et al. Efficacy and safety of a dual inhibitor of 5-alpha-reductase types 1 and 2 (dutasteride) in men with benign prostatic hyperplasia. *Urology* 2002; 60: 434-441.
- 3 IM Thompson et al. The influence of finasteride on the development of prostate cancer. *New England Journal of Medicine* 2003; 349: 213-222.

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